In Vitro to In Vivo Extrapolation: Optimizing Parameters for Improved Predictions

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In vitro to in vivo extrapolation (IVIVE) is necessary for utilizing data from in vitro high-throughput assays in risk assessment. We evaluated the impact of key pharmacokinetic parameters, dosimetry, and modeling approaches for IVIVE of estrogenic activity. Data for ten chemicals with estrogen receptor (ER) agonist activity were obtained from 16 ToxCast/Tox21 assays mapping to key events along the ER pathway. One-compartment and multi-compartment physiologically based pharmacokinetic models were used to estimate daily equivalent administered dose (EAD) that would result in blood concentrations equivalent to the lowest effective concentrations (LECs) in these in vitro assays. For each chemical, the estimated lowest or median EADs were compared to the lowest or median lowest effect level (LEL) across uterotrophic assays. We examined the influence of fraction of unbound chemical (Fub) and hepatic clearance on EAD estimates by systematically varying these parameters across a range of observed values. To better estimate the free fraction, we applied a Fub adjustment method to estimate EADs that would result in blood concentrations of free chemical equivalent to in vitro LECs. Our models performed well in predicting in vivo LELs from in vitro effective concentrations for the majority of chemicals tested, particularly after Fub adjustment. This study demonstrates an optimal approach for using in vitro data to quantitatively predict in vivo effects. *This project was funded in whole or in part with Federal funds from the NIEHS, NIH under Contract No.HHSN27320140003C.*

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1. Endocrine disruptor chemicals
2. Pharmacokinetic/dynamic models
3. High-throughput PBPK models